ONLINE FIRST

Choice of Initial Combination Antiretroviral Therapy in Individuals With HIV Infection

Determinants and Outcomes

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Background: Current guidelines give recommendations for preferred combination antiretroviral therapy (cART). We investigated factors influencing the choice of initial cART in clinical practice and its outcome.

Methods: We analyzed treatment-naive adults with human immunodeficiency virus (HIV) infection participating in the Swiss HIV Cohort Study and starting cART from January 1, 2005, through December 31, 2009. The primary end point was the choice of the initial antiretroviral regimen. Secondary end points were virologic suppression, the increase in CD4 cell counts from baseline, and treatment modification within 12 months after starting treatment.

Results: A total of 1957 patients were analyzed. Tenofovir-emtricitabine (TDF-FTC)–efavirenz was the most frequently prescribed cART (29.9%), followed by TDF-FTC-lopinavir/r (16.9%), TDF-FTC-atazanavir/r (12.9%), zidovudine-lamivudine (ZDV-3TC)–lopinavir/r (12.8%), and abacavir/lamivudine (ABC-3TC)–efavirenz (5.7%). Differences in prescription were noted among different Swiss HIV Cohort Study sites ($P < .001$). In multivariate analysis, compared with TDF-FTC-efavirenz, starting TDF-FTC-lopinavir/r was associated with prior AIDS (relative risk ratio, 2.78; 95% CI, 1.78-4.35), HIV-RNA greater than 100 000 copies/mL (1.53; 1.07-2.18), and CD4 greater than 350 cells/μL (1.67; 1.04-2.70); TDF-FTC-atazanavir/r with a depressive disorder (1.77; 1.04-3.01), HIV-RNA greater than 100 000 copies/mL (1.54; 1.05-2.25), and an opiate substitution program (2.76; 1.09-7.00); and ZDV-3TC-lopinavir/r with female sex (3.89; 2.39-6.31) and CD4 cell counts greater than 350 cells/μL (4.50; 2.58-7.86). At 12 months, 1715 patients (87.6%) achieved viral load less than 50 copies/mL and CD4 cell counts increased by a median (interquartile range) of 173 (89-269) cells/μL. Virologic suppression was more likely with TDF-FTC-efavirenz, and CD4 increase was higher with ZDV-3TC-lopinavir/r. No differences in outcome were observed among Swiss HIV Cohort Study sites.

Conclusions: Large differences in prescription but not in outcome were observed among study sites. A trend toward individualized cART was noted suggesting that initial cART is significantly influenced by physician's preference and patient characteristics. Our study highlights the need for evidence-based data for determining the best initial regimen for different HIV-infected persons.

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COMBINATION ANTIRETROviral therapy (cART) has improved the prognosis of human immunodeficiency virus (HIV) infection close to normal life expectancy.[1-5] More than 20 antiretroviral drugs are currently available with different efficacy, pill burden, and potential adverse effects.[6-8] The presence of transmitted HIV drug resistance, comorbidities, potential drug-drug interactions, expected adverse effects, and socioeconomic barriers should be considered before starting cART.[3,9-12] International guidelines recommend preferred antiretroviral regimens to guide physicians.[6-8] Preferred regimens are those shown to have optimal and durable virologic efficacy as well as favorable tolerability and toxicity profiles in randomized controlled trials. Studies on initiating

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cART in different populations exist, mostly focusing on the treatment efficacy, discontinuation, and toxicity of specific regimens. In clinical practice, cART may be prescribed differently to groups of patients with varying baseline characteristics and prognoses, giving rise to chan-

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neling bias. Channeling bias is a form of allocation bias in which physicians tend to prescribe treatment, and in particular, newer drugs, on the basis of a patient's prognosis, leading to a biased estimate of treatment efficacy. Approximately 30% of patients change their antiretroviral regimen within the first year of cART,[13] mainly because of toxicity. It is desirable that this high proportion of treatment changes be further reduced. Choice of treatment may be influenced by HIV stage, comorbidities, comedication with potential drug-drug interactions, pregnancy or pregnancy potential, expected cART toxicity, and results of genotypic resistance testing. Also, the physician's preference and the patient's wish for a certain drug may play an important role. Factors that finally determine the choice of the initial antiretroviral regimen are poorly studied. In a retrospective cohort analysis investigating initial cART in 150 HIV-infected individuals,[14] preliminary data showed that clinical and sociodemographic factors predict the choice of initial cART. A recent evaluation within the Swiss HIV Cohort Study (SHCS) revealed that more than 200 different antiretroviral regimens were prescribed from August 1, 1998, through December 31, 2007, whereas the 10 most frequent regimens covered two-thirds of patients.[15] To our knowledge, there are no other studies investigating this question.

The aim of this study was to investigate factors that influence the choice of the initial cART regimen in treatment-naive HIV-infected individuals and their effect on outcome—that is, virologic suppression, immunologic recovery, and time to treatment modification.

METHODS

STUDY DESIGN

The SHCS[16] is a large prospective cohort study with continuous enrollment of HIV-infected individuals aged 16 years or older followed up in HIV outpatient clinics of 7 Swiss hospitals (Basel, Bern, Geneva, Lausanne, Lugano, S. Gallen, and Zurich) and by associated physicians. Basic sociodemographic characteristics, data on the clinical course, hepatitis coinfection, antiretroviral treatment, comedication, cardiovascular risk factors, and immunologic and virologic information are collected at study enrollment and every 6 months thereafter on standardized data collection forms. AIDS-defining diseases are recorded using the 1993 revised clinical definition of AIDS from the Centers for Disease Control and Prevention.[17] For the present analysis, we used the SHCS database extract of October 2011.

STUDY POPULATION

Antiretroviral-naive HIV-infected individuals participating in the SHCS who started cART from January 1, 2005, through December 31, 2009, and who had a potential follow-up of at least 12 months were eligible for this study. Exclusion criteria were pregnancy, because only a few antiretroviral regimens are recommended in this setting owing to the potential for teratogenicity and the lack of data on the safety of specific drugs in pregnancy,[7,8,18,19] and starting cART more than 3 months before enrollment in the SHCS because detailed data on laboratory and comorbidities were not available.

DEFINITIONS

Combination antiretroviral therapy was defined as an antiretroviral regimen containing at least 3 drugs—that is, 2 nucleoside/nucleotide reverse-transcriptase inhibitors in combination with either a nonnucleoside reverse-transcriptase inhibitor (NNRTI), an integrase inhibitor, or a protease inhibitor (PI). Antiretroviral regimens were classified in accordance with currently recommended regimens.[6-8] Virologic suppression was defined as achieving HIV-RNA less than 50 copies/mL at 12 months. Cutoffs for individual cardiovascular risk factors were based on those by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults[20]; the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in Adults; and the American Diabetes Association.[21] Family history was defined as a first-degree relative with a cardiovascular event before the age of 50 years. The Framingham score,[22] estimating the 10-year risk of cardiovascular events, was calculated for all individuals at the time of starting cART. The glomerular filtration rate was calculated based on the Cockcroft-Gault equation.[23]

STATISTICAL ANALYSIS

The primary end point was the choice of the initial antiretroviral regimen according to 6 categories—that is, the 5 most frequently prescribed regimens (tenofovir-emtricitabine [TDF-FTC] combined with atazanavir/r, lopinavir/r, or efavirenz; zidovudine-lamivudine [ZDV-3TC] combined with lopinavir/r; and abacavir [ABC]–3TC combined with efavirenz) and "other regimen." Secondary end points were virologic suppression, the increase in CD4 cell counts, and cART modification in the first year. Basic sociodemographic characteristics, comorbidities, cardiovascular risk, comedication, CD4 cell count, HIV viral load, and cART were compared using the χ^2 test or the Fisher exact test for categorical variables and the Mann-Whitney test or the Kruskal-Wallis test for continuous variables. A multinomial logistic regression model was fit to investigate sociodemographic and clinical factors associated with the choice of the initial antiretroviral regimen. Binomial logistic regression was used to explore predictors of achieving HIV-RNA less than 50 copies/mL at 12 months. Multiple linear regression models were used to estimate the increase in CD4 cell counts from baseline, and Cox proportional hazards regression was used to assess the time to treatment modification within the first year. Heterogeneity introduced by different SHCS sites was accounted for by including the study site as a fixed effect in the models and by calculating Huber-White robust standard errors for intrasite correlation. A competing risk regression model by the method of Fine and Gray[24] was fitted to compare the 2 most frequently used regimens in the last 2 study years—that is, TDF-FTC combined with either efavirenz or atazanavir/r, where the primary end point was the time to achieve HIV-RNA less than 50 copies/mL and the competing risk was modification of the initial antiretroviral regimen. All analyses were performed using Stata software, version 11 (Stata Corp).

RESULTS

STUDY POPULATION

Among more than 16 000 participants of the SHCS, 2509 antiretroviral-naive HIV-infected individuals started cART from January 1, 2005, through December 31, 2009. Of these, we excluded 104 pregnant women and 448 pa-

Table 1. Baseline Characteristics of 1957 Study Participants According to the Initial Antiretroviral Regimen[a]

Variable	TDF-FTC and Efavirenz (n = 586)	TDF-FTC and Lopinavir/r (n = 331)	TDF-FTC and Atazanavir/r (n = 253)	ZDV-3TC and Lopinavir/r (n = 251)	ABC-3TC and Efavirenz (n = 111)	Other Regimen (n = 425)	*P* Value
Age, median (IQR), y	40 (33-46)	41 (34-47)	40 (34-46)	36 (30-43)	40 (34-45)	39 (33-47)	<.001
Male sex	468 (79.9)	255 (77.0)	199 (78.7)	173 (68.9)	87 (78.4)	294 (69.2)	<.001
White race	441 (75.3)	254 (76.7)	205 (81.0)	195 (77.7)	76 (68.5)	325 (76.5)	.18
BMI, median (IQR)	23 (21-26)	23 (21-26)	23 (21-26)	23 (21-26)	23 (20-25)	23 (21-26)	.73
Transmission risk							
MSM	284 (48.5)	159 (48.0)	127 (50.2)	109 (43.4)	47 (42.3)	178 (41.9)	.003
Heterosexual	233 (39.8)	125 (37.8)	83 (32.8)	105 (41.8)	52 (46.9)	176 (41.4)	
IDU	34 (5.8)	35 (10.6)	37 (14.6)	26 (10.4)	9 (8.1)	45 (10.6)	
Other	35 (6.0)	12 (3.6)	6 (2.4)	11 (4.4)	3 (2.7)	26 (6.1)	
Current IDU	16 (2.7)	15 (4.5)	17 (6.7)	9 (3.6)	6 (5.4)	20 (4.7)	.15
Prior AIDS-defining condition	87 (14.9)	85 (25.7)	28 (11.1)	45 (17.9)	14 (12.6)	76 (17.9)	<.001
HBV, HBs-antigen positive	28 (4.8)	23 (7.0)	18 (7.1)	4 (1.6)	1 (0.9)	3 (0.7)	<.001
HCV, HCV antibodies	73 (12.5)	49 (14.8)	56 (22.1)	39 (15.5)	11 (9.9)	67 (15.8)	.008
Depressive disorder	51 (8.7)	30 (9.1)	32 (12.7)	10 (4.0)	5 (4.5)	46 (10.8)	.006
Framingham 10-y risk >20%	27 (4.6)	20 (6.0)	8 (3.2)	4 (1.6)	1 (0.9)	12 (2.8)	.02
CD4 cell count, median (IQR), cells/μL	244 (156-319)	228 (118-325)	233 (158-314)	278 (164-408)	269 (173-335)	240 (150-319)	.004
HIV-RNA, median (IQR), $\log_{10}$ copies/mL	4.7 (4.2-5.1)	4.8 (4.3-5.4)	4.7 (4.2-5.2)	5.0 (4.5-5.7)	4.6 (4.1-5.1)	4.8 (4.3-5.3)	<.001
Creatinine clearance <80 mL/min	12 (2.6)	7 (2.9)	1 (0.5)	6 (3.5)	4 (4.6)	8 (2.4)	.36
Treatment for cardiovascular disease	69 (11.8)	26 (7.9)	31 (12.3)	17 (6.8)	13 (11.7)	58 (13.7)	.07
Treatment for mycobacterial infection	32 (5.5)	10 (3.0)	3 (1.2)	7 (2.8)	4 (3.6)	18 (4.2)	.08
Treatment for viral HCV	6 (1.0)	3 (0.9)	2 (0.8)	1 (0.4)	2 (1.8)	1 (0.2)	.52
Opiate substitution program	14 (2.4)	17 (5.1)	25 (9.9)	6 (2.4)	8 (7.2)	24 (5.7)	<.001
PCP prophylaxis	170 (29.0)	115 (34.7)	66 (26.1)	63 (25.1)	30 (27.1)	137 (32.2)	.08
Calendar period							
2005-2006	206 (35.2)	112 (33.8)	69 (27.3)	120 (47.8)	14 (12.6)	141 (33.2)	<.001
2007-2008	225 (38.4)	145 (43.8)	103 (40.7)	99 (39.4)	78 (70.3)	181 (42.6)	
2009	155 (26.4)	74 (22.4)	81 (32.0)	32 (12.8)	19 (17.1)	103 (24.2)	
SHCS center[b]							
A	(35.5)	(50.1)	(50.6)	(63.3)	(14.4)	(32.0)	<.001
B	(10.6)	(10.9)	(10.3)	(5.2)	(14.4)	(11.3)	
C	(15.2)	(6.6)	(13.4)	(8.0)	(46.0)	(22.4)	
D	(13.3)	(7.3)	(11.4)	(4.4)	(5.4)	(7.1)	
E	(22.3)	(11.8)	(11.1)	(11.5)	(9.9)	(11.8)	
F	(1.9)	(4.2)	(0.4)	(0.8)	(0.9)	(2.3)	
G	(1.2)	(9.1)	(2.8)	(6.8)	(9.0)	(13.2)	

Abbreviations: ABC, abacavir; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FTC, emtricitabine; HBs, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injecting drug use; IQR, interquartile range; MSM, men who have sex with men; PCP, *Pneumocystis jirovecii* pneumonia; SHCS, Swiss HIV Cohort Study; TDF, tenofovir; ZDV, zidovudine; 3TC, lamivudine.

[a] Data are given as number (percentage) unless otherwise indicated.

[b] Raw data are omitted to prevent identification of study site.

tients who started cART more than 3 months before enrollment in the SHCS. The final analysis was performed on 1957 patients. Baseline characteristics according to the initial antiretroviral regimen are shown in **Table 1**.

CHOICE OF THE INITIAL ANTIRETROVIRAL REGIMEN

The most frequently prescribed regimen consisted of TDF-FTC-efavirenz (586 [29.9%]), followed by TDF-FTC- lopinavir/r (331 [16.9%]) and TDF-FTC- atazanavir/r (253 [12.9%]). Other regimens were given less frequently (Table 1). Large differences in the prescription of cART were noted among different SHCS sites ($P < .001$) and over time ($P < .001$), with TDF-FTC-efavirenz and TDF-FTC-atazanavir/r the 2 most commonly prescribed regimens in the last 2 study years. Prescription of the atazanavir/r–based regimen increased earlier in one site compared with the other, but this difference was compensated over time. In multivariate analysis (**Table 2**), treatment with TDF-FTC-lopinavir/r, compared with TDF-FTC-efavirenz, was associated with a prior AIDS-defining condition (relative risk ratio [RRR] 2.78; 95% CI, 1.78-4.35), CD4 cell counts greater than 350 (1.67; 1.04-2.70), and HIV-RNA greater than 100 000 copies/mL (1.53; 1.07-2.18). Treatment with TDF-FTC-atazanavir/r was more likely prescribed in those with depressive disorders (RRR, 1.77; 95% CI, 1.04-3.01), those with HIV-RNA greater than 100 000 copies/mL (1.54; 1.05-2.25), and those enrolled in an opiate substitution program (2.76; 1.09-7.00). Starting ZDV-3TC-lopinavir/r was more likely in women (RRR, 3.89; 95%

Table 2. Multivariate RRRs for Determinants of the Choice of the Initial cART Regimen Relative to TDF-FTC Combined With Efavirenz in 1957 Patients

Variable	TDF-FTC and Lopinavir/r		TDF-FTC and Atazanavir/r		ZDV-3TC and Lopinavir/r		ABC-3TC and Efavirenz		Other Regimen	
	RRR (95% CI)	*P* Value	RRR (95% CI)	*P* Value	RRR (95% CI)	*P* Value	RRR (95% CI)	*P* Value	RRR (95% CI)	*P* Value
Age, per 10-y older	1.06 (0.88-1.28)	.52	1.02 (0.85-1.23)	.81	0.80 (0.63-1.02)	.08	0.97 (0.75-1.25)	.82	0.96 (0.81-1.14)	.63
Female sex	1.57 (0.85-1.64)	.12	1.39 (0.87-2.22)	.16	3.89 (2.39-6.31)	<.001	0.87 (0.45-1.68)	.69	1.99 (1.33-2.97)	.001
Nonwhite race	1.01 (0.65-1.62)	.90	0.86 (0.52-1.41)	.55	1.00 (0.61-1.65)	>.99	1.97 (0.90-2.18)	.14	0.82 (0.53-1.25)	.35
Current IDU	1.55 (0.57-4.25)	.39	1.38 (0.50-3.78)	.53	1.54 (0.46-5.17)	.48	1.34 (0.44-4.15)	.61	1.54 (0.62-3.79)	.35
Prior AIDS-defining condition	2.78 (1.78-4.35)	<.001	0.89 (0.48-1.66)	.72	1.54 (0.85-2.75)	.15	0.89 (0.41-1.95)	.79	1.23 (0.77-1.96)	.38
HBV, HBs-antigen positive	1.22 (0.61-2.44)	.58	1.43 (0.70-2.89)	.32	0.45 (0.15-1.35)	.16	0.15 (0.03-1.35)	.07	0.16 (0.05-0.57)	.004
HCV, HCV antibodies	1.09 (0.63-1.89)	.75	1.63 (0.96-2.76)	.07	1.49 (0.82-2.70)	.19	0.64 (0.28-1.48)	.30	0.99 (0.60-1.63)	.97
Depressive disorder	1.43 (0.82-2.51)	.21	1.77 (1.04-3.01)	.04	0.60 (0.25-1.43)	.25	0.56 (0.17-1.90)	.36	1.61 (0.97-2.68)	.08
Framingham 10-y risk >20%	1.42 (0.66-3.05)	.37	0.50 (0.18-1.40)	.19	1.06 (0.28-3.99)	.94	0.33 (0.04-2.51)	.29	0.68 (0.28-1.65)	.39
CD4 cell count										
<200	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
200-350	0.99 (0.67-1.46)	.96	1.02 (0.67-1.55)	.93	1.50 (0.91-2.47)	.11	1.14 (0.65-1.98)	.65	1.01 (0.71-1.44)	.95
>350	1.67 (1.04-2.70)	.04	1.34 (0.80-2.26)	.27	4.50 (2.58-7.86)	<.001	1.80 (0.86-3.79)	.12	1.43 (0.92-2.22)	.11
HIV-RNA >100 000 copies/mL	1.53 (1.07-2.18)	.02	1.54 (1.05-2.25)	.03	3.19 (2.13-4.77)	<.001	1.42 (0.81-2.50)	.23	1.56 (1.12-2.17)	.008
Creatinine clearance <80 mL/min	0.68 (0.23-1.99)	.48	0.19 (0.02-1.57)	.12	1.27 (0.34-4.78)	.72	1.73 (0.43-6.92)	.44	0.69 (0.26-1.86)	.46
Treatment for cardiovascular disease	0.72 (0.39-1.33)	.29	1.03 (0.56-1.87)	.93	0.56 (0.33-1.33)	.11	1.05 (0.46-2.39)	.92	1.53 (0.91-2.56)	.11
Treatment for mycobacterial infection	0.32 (0.10-1.08)	.07	0.46 (0.13-1.62)	.23	0.50 (0.22-1.14)	.10	0.65 (0.18-2.32)	.51	0.88 (0.39-2.00)	.76
Opiate substitution program	1.33 (0.49-3.59)	.58	2.76 (1.09-7.00)	.03	1.00 (0.38-2.63)	>.99	2.79 (0.92-8.45)	.07	2.61 (0.68-3.83)	.28
Calendar period										
2005-2006	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
2007-2008	1.53 (0.87-1.62)	.04	1.37 (0.95-1.62)	.24	1.05 (0.68-1.61)	.84	9.37 (4.10-21.4)	<.001	1.58 (1.09-2.28)	.02
2009	1.05 (0.68-1.62)	.82	1.56 (0.61-1.26)	.48	0.45 (0.26-0.76)	.003	2.69 (1.09-6.64)	.03	1.14 (0.77-1.69)	.51
SHCS center										
A	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
B	0.47 (0.27-0.81)	.006	0.65 (0.36-1.17)	.15	0.21 (0.09-0.50)	<.001	3.28 (1.39-7.75)	.007	0.94 (0.58-1.52)	.80
C	0.28 (0.15-0.51)	<.001	0.48 (0.28-0.82)	.007	0.29 (0.15-0.56)	<.001	7.86 (3.78-16.4)	<.001	1.16 (0.75-1.77)	.50
D	0.34 (0.17-0.70)	.003	0.62 (0.31-1.23)	.17	0.20 (0.08-0.51)	.001	0.95 (0.26-3.43)	.93	0.55 (0.30-1.03)	.06
E	0.29 (0.17-0.49)	<.001	0.29 (0.17-0.49)	<.001	0.22 (0.13-0.38)	<.001	0.98 (0.38-2.57)	.97	0.27 (0.16-0.46)	<.001
F	0.93 (0.34-2.59)	.90	0.18 (0.02-1.52)	.12	0.12 (0.02-0.92)	.04	1.79 (0.19-17.1)	.61	1.13 (0.43-2.94)	.80
G	3.05 (1.21-7.70)	.02	0.56 (0.14-2.26)	.41	2.02 (0.70-5.85)	.19	10.2 (2.67-39.6)	.001	8.26 (3.51-19.5)	<.001

Abbreviations: ABC, abacavir; cART, combination antiretroviral therapy; FTC, emtricitabine; HBs, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injecting drug use; RRR, relative risk ratio; SHCS, Swiss HIV Cohort Study; TDF, tenofovir; ZDV, zidovudine; 3TC, lamivudine.

CI, 2.39-6.31), those with CD4 cell counts greater than 350 (4.50; 2.58-7.86), and those with HIV viral load greater than 100 000 copies/mL (3.19; 2.13-4.77). Treatment with ABC-3TC-efavirenz was given more recently (RRR, 9.37; 95% CI, 4.10-21.4, after 2007), whereas alternative regimens were more likely prescribed in women, patients with hepatitis B virus coinfection, those with HIV viral load greater than 100 000 copies/mL, and after 2007.

The **Figure** illustrates the probability of choosing specific cART regimens according to particular clinical settings. For example, active injecting drug users were more likely to start TDF-FTC-atazanavir/r (21.3% vs 12.9% probability), and patients with a prior AIDS-defining condition were more likely to start TDF-FTC-lopinavir/r (26.7% vs 14.2%). Individuals with high cardiovascular risk, as measured by a Framingham score greater than 20%, were started on TDF-FTC-efavirenz (39.3% vs 30.7%) but less frequently on ABC-3TC-efavirenz (1.6% vs 6.1%).

OUTCOMES AT 12 MONTHS AFTER cART INITIATION

Overall, 1715 patients (87.6%) starting cART achieved virologic suppression (<50 copies/mL) at 12 months. In an intention-to-treat approach, virologic response in patients was the highest with TDF-FTC-efavirenz (92.2%), followed by ABC-3TC-efavirenz (90.1%), TDF-FTC-atazanavir/r (86.1%), TDF-FTC-lopinavir/r (86.1%), and ZDV-3TC-lopinavir/r (83.3%) (P = .001). In the on-treatment analysis, 96.6% of patients receiving TDF-FTC-efavirenz achieved virologic suppression vs 85.9% of those receiving ZDV-3TC-lopinavir/r (P = .005). In the multivariate analysis (**Table 3**), patients with HIV viral load greater than 100 000 copies/mL (odds ratio, 0.43; 95% CI, 0.31-0.61) and those who discontinued cART (0.14; 0.09-0.22) were less likely to achieve virologic suppression. No differences in virologic response were observed among antiretroviral regimens and study sites.

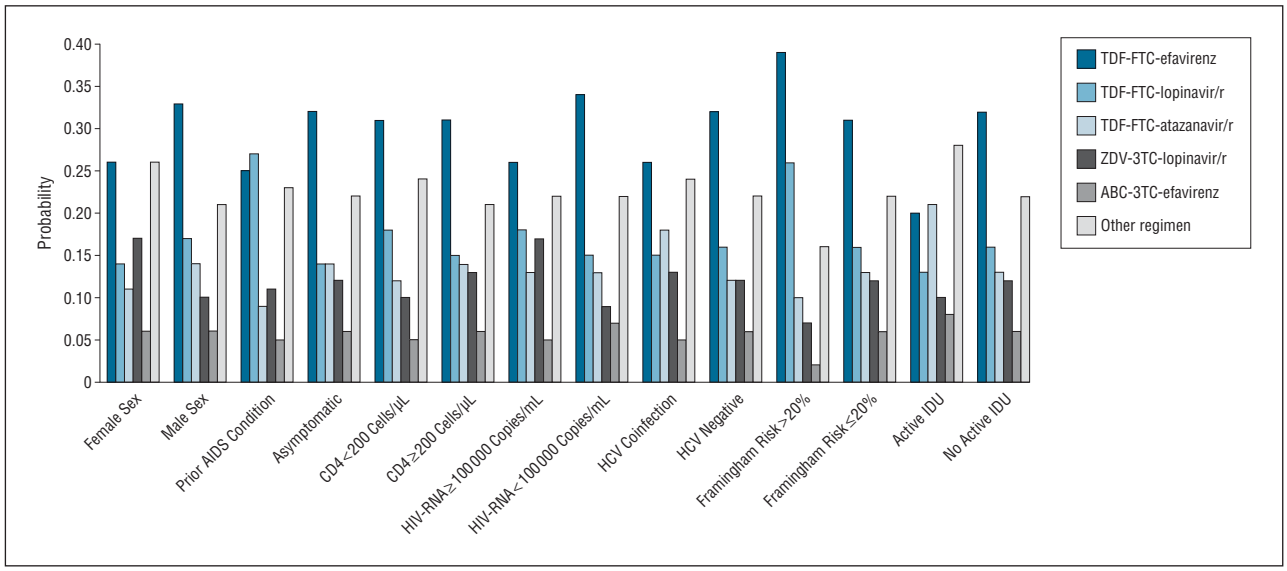

Figure. Probability of the initial combination antiretroviral therapy regimen according to frequent clinical settings fitting the multivariate multinomial logistic model adjusted for sociodemographic characteristics, comorbidities, human immunodeficiency virus (HIV)–related factors (prior AIDS-defining condition, CD4 cell counts, and viral load), Swiss HIV Cohort Study site, and calendar year. ABC indicates abacavir; FTC, emtricitabine; HCV, hepatitis C virus; IDU, injecting drug use; TDF, tenofovir; ZDV, zidovudine; 3TC, lamivudine.

The overall median (interquartile range) increase in CD4 cell counts within the first year of cART was 173 (89-269) cells/µL, being the highest in patients treated with ZDV-3TC-lopinavir/r (209 [107-326] cells/µL), followed by TDF-FTC-lopinavir/r (177 [97-284] cells/µL), ABC-3TC-efavirenz (173 [96-257] cells/µL), TDF-FTC-atazanavir/r (168 [96-279] cells/µL), and TDF-FTC-efavirenz (158 [84-240] cells/µL) ($P = .001$). After adjustment for sociodemographic characteristics, comorbidities, comedication, HIV stage, CD4 cell count at baseline, viral load at 1 year, calendar period, and study site, better immunologic recovery was associated with lopinavir/r combined with either TDF-FTC or ZDV-3TC (mean [95% CI] CD4 cell count increase from baseline of , 49 [25-73] cells/µL and 73 [45-100] cells/µL, respectively), higher CD4 cell counts at baseline (82 [74-89] per 100 CD4 cells/µL increase), and achievement of virologic suppression of less than 50 copies/mL at 1 year (57 [31-83] cells/µL). Lower immunologic recovery was noted in older patients (mean [95% CI] change in CD4 cell count from baseline of –16 [–25 to –9] cells/µL, per 10-year increase), coinfection with hepatitis C (–43 [–66 to –20] cells/µL), and prophylaxis for *Pneumocystis jirovecii* pneumonia with trimethoprim-sulfamethoxazole (–58 [–77 to –38] cells/µL).

During the first year, 615 patients (31.4%) switched their initial treatment to another regimen and 231 (11.8%) discontinued cART for at least 4 weeks, corresponding to 44.9 (95% CI, 41.7-48.4) treatment modifications per 100 person-years. Patients treated with ZDV-3TC-lopinavir/r had the highest rate of treatment changes (86.5 [95% CI, 72.2-101.2] per 100 person-years), followed by TDF-FTC-efavirenz (28.4 [24.1-33.5]), ABC-3TC-efavirenz (28.4 [19.3-41.6]), and TDF-FTC-atazanavir/r (32.1 [25.3-40.7]) ($P < .001$). Treatment modification rates were similar across SHCS sites ($P = .12$). After adjustment for sociodemographic characteristics, HIV clinical stage, CD4 cell count, HIV-RNA, comorbidities, comedication, calendar period, and study site, treatment modification was more likely in women (hazard ratio, 1.26 [95% CI, 1.05-1.51]), with CD4 greater than 350 at baseline (1.29 [1.05-1.60]), and with TDF-FTC-lopinavir/r (1.88 [1.47-2.39]) or ZDV-3TC-lopinavir/r (2.65 [2.06-3.42]).

No differences between TDF-FTC-efavirenz and TDF-FTC-atazanavir/r were found after adjustment for sociodemographic characteristics, HIV clinical stage, CD4 cell count, HIV viral load, comorbidities, comedication, and calendar year in an intention-to-treat approach, in which lack of virologic suppression or treatment modification were considered as failures, and in a multivariate competing risk regression model.

COMMENT

This study, involving 1957 treatment-naive HIV-infected individuals who started cART from January 1, 2005, through December 31, 2009, in a large cohort study, illustrates a trend toward individualized cART and large differences in the prescription of cART among study sites, suggesting that the choice of the initial regimen is driven by clinical and demographic patient characteristics as well as by physicians' preferences. It is reassuring that the outcome of cART in terms of combined virologic response, treatment modification, and immunologic recovery during the first year of treatment did not differ among the most often prescribed antiretroviral regimens and SHCS sites. In fact, in an earlier evaluation within the SHCS, only regimens that violated current guidelines were associated with a higher risk of failure.[15]

Detailed analysis of the 2 most frequently prescribed regimens in the last study period—that is, TDF-FTC combined with either efavirenz or atazanavir/r—demonstrated that better virologic response of the efavirenz-based regimen in the univariate analysis was not

Table 3. Univariate and Multivariate Analyses of Predictors of Virologic Suppression Less Than 50 Copies/mL at 12 Months After Starting cART

	Univariate Analysis		Multivariate Analysis	
Variable	OR (95% CI)	*P* Value	OR (95% CI)[a]	*P* Value
Age, per 10-y older	1.02 (0.88-1.18)	.80	0.99 (0.83-1.18)	.93
Female sex	0.80 (0.57-1.11)	.19	0.81 (0.55-1.20)	.29
Nonwhite race	0.96 (0.67-1.35)	.81	0.79 (0.51-1.23)	.29
Current IDU	0.51 (0.28-0.92)	.03	0.75 (0.36-1.54)	.43
Prior AIDS-defining condition	0.80 (0.55-1.16)	.24	0.99 (0.64-1.54)	.97
HBV coinfection, HBs-antigen positive	1.63 (0.65-4.09)	.30	1.42 (0.54-3.74)	.48
HCV coinfection, HCV antibodies	0.71 (0.48-1.14)	.10	0.96 (0.57-1.64)	.89
Depressive disorder	1.27 (0.72-2.24)	.41	1.20 (0.65-2.23)	.55
Framingham 10-y risk >20%	0.77 (0.38-1.58)	.48	0.58 (0.25-1.35)	.21
CD4 cell count				
<200	1 [Reference]		1 [Reference]	
200-350	1.41 (0.96-1.99)	.06	1.27 (0.87-1.87)	.22
>350	0.81 (0.56-1.19)	.29	0.84 (0.55-1.29)	.42
HIV-RNA >100 000 copies/mL	0.47 (0.35-0.63)	<.001	0.43 (0.31-0.61)	<.001
Creatinine clearance <80 mL/min	0.95 (0.33-2.71)	.92	1.39 (0.46-4.25)	.56
Opiate substitution program	0.49 (0.38-0.87)	.01	0.51 (0.24-1.09)	.08
cART				
TDF-FTC and efavirenz	1 [Reference]		1 [Reference]	
TDF-FTC and lopinavir/r	0.59 (0.36-0.98)	.04	0.78 (0.46-1.33)	.36
TDF-FTC and atazanavir/r	0.53 (0.32-0.90)	.02	0.66 (0.39-1.14)	.14
ZDV-3TC and lopinavir/r	0.36 (0.22-0.58)	<.001	0.60 (0.34-1.16)	.18
ABC-3TC and efavirenz	0.74 (0.35-1.59)	.28	0.73 (0.31-1.69)	.46
Other regimen	0.48 (0.31-0.75)	.001	0.67 (0.41-1.08)	.10
Switch of cART to another regimen	0.73 (0.51-1.05)	.09	0.81 (0.54-1.21)	.30
Discontinuation of cART	0.13 (0.09-0.19)	<.001	0.14 (0.09-0.22)	<.001
Calendar period				
2005-2006	1 [Reference]		1 [Reference]	
2007-2008	1.17 (0.79-1.73)	.43	0.91 (0.62-1.35)	.64
2009	1.05 (0.38-1.62)	.84	0.98 (0.44-1.23)	.11
SHCS center				
A	1 [Reference]		1 [Reference]	
B	0.68 (0.43-1.09)	.11	0.65 (0.39-1.09)	.10
C	1.09 (0.69-1.73)	.71	1.11 (0.67-1.86)	.68
D	0.97 (0.56-1.69)	.93	0.94 (0.50-1.75)	.83
E	1.10 (0.69-1.77)	.68	1.15 (0.69-1.89)	.60
F	2.00 (0.47-8.46)	.35	2.32 (0.45-11.9)	.31
G	0.64 (0.38-1.12)	.12	0.70 (0.38-1.30)	.26

Abbreviations: ABC, abacavir; cART, combination antiretroviral therapy; FTC, emtricitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injecting drug use; OR, odds ratio; SHCS, Swiss HIV Cohort Study; TDF, tenofovir; ZDV, zidovudine; 3TC, lamivudine.
[a] Adjusted for all variables listed.

explained by different prognostic parameters and channeling of patients with higher HIV viral load to a PI-based antiretroviral regimen. The intention-to-treat approach, in which lack of virologic suppression and treatment modification were considered as treatment failures, showed no difference between these 2 antiretroviral regimens. These findings highlight the different options for initial cART and the individualized approach that includes the physician's and patient's preference in choosing the best-suited antiretroviral regimen.

Tenofovir-emtricitabine-efavirenz is the first cART coformulated in a single pill daily and is currently the most frequently prescribed regimen in developed countries. However, not all patients are appropriate candidates for an efavirenz-based therapy because of potential adverse effects, in particular depressive disorders and drug interaction with methadone.[25] Indeed, patients with a depressive disorder and those enrolled in an opiate substitution program were more likely to start with TDF-FTC-atazanavir/r than TDF-FTC-efavirenz. Also, NNRTIs have a relatively low barrier to resistance,[26,27] suggesting that boosted PI-containing regimens might be preferred in patients at risk of suboptimal adherence, such as those with active drug use or psychiatric comorbidity. Women were more likely to start ZDV-3TC-lopinavir/r compared with TDF-FTC-efavirenz. Despite the fact that efavirenz has not been demonstrated to be teratogenic in humans,[28] it is not recommended in sexually active women of childbearing age who are not using reliable contraception owing to teratogenicity reported in nonhuman primates. In a subgroup analysis (data not shown), differences in cART between sexes were not observed in patients older than 40 years anymore. Also, higher rates of adverse events in the central nervous system were reported in women,[13] possibly related to lower weight and higher efavirenz plasma levels. Our data indicate that these circumstances probably play a role for prescription in women.

There are many options for selecting a boosted PI. For years, lopinavir/r has been the standard PI, on the basis of antiviral efficacy and long-term durability of response.[29,30] Atazanavir/r has the lowest daily pill count of boosted PIs, and it is associated with less effect on plasma lipids than lopinavir/r. Virologic activity of atazanavir/r was shown to be similar to lopinavir/r at 48 weeks[31] and higher than lopinavir/r in an intention-to-treat analysis at 96 weeks because of a higher rate of treatment discontinuations in the lopinavir/r arm.[32] In our study, patients with a high cardiovascular risk were not more likely to start atazanavir/r, but they tended not to start abacavir-containing regimens, reflecting the recommendation in guidelines for not initiating abacavir in patients at higher risk of myocardial infarction.[6-8,33] Patients who were already treated for a cardiovascular disease at baseline were less likely to receive a lopinavir/r-based regimen, presumably reflecting concerns on lopinavir/r-related dyslipidemia.

Among backbones, TDF-FTC was shown to have superior virologic activity and fewer treatment discontinuations than ZDV-3TC,[34] and ABC-3TC had similar virologic efficacy but higher CD4 increase compared with ZDV-3TC when combined with efavirenz.[35] Among patients with baseline HIV-RNA above 100 000 copies/mL, TDF-FTC had better virologic activity compared with ABC-3TC when combined with efavirenz or atazanavir/r.[36-38] In another trial,[39] efficacy of ABC-3TC was noninferior to TDF-FTC when combined with lopinavir/r regardless of baseline HIV viral load. In our study population, however, patients with higher HIV viral load were more likely to be started on PI-based regimens, possibly reflecting lower risk for resistance in PIs with high viral load and suboptimal adherence.[27] Moreover, patients with a prior AIDS-defining condition, indicating far advanced HIV infection, were more likely to be started on a lopinavir/r-based regimen. Our study confirms earlier results that cART including an NNRTI yielded the best results in terms of virologic suppression, whereas PI-based regimens showed better immunologic recovery.[26,40]

We acknowledge some limitations. Because of the small number of patients started on most recently recommended first-line regimens—that is, darunavir/r and raltegravir, we could not include these drugs in our analysis. Data on genotypic resistance testing and HLA B*5701 were not available for the present analysis. However, in Switzerland, the prevalence of primary NNRTI resistance is very low,[41] and it is therefore unlikely that drug resistance is a main reason for selecting the initial antiretroviral regimen. Screening for HLA B*5701 is routinely performed in Switzerland before starting abacavir-containing cART, but the prevalence of this mutation is very low.[42] Moreover, we could not assess whether choice was more dependent on physicians' characteristics, such as experience in HIV medicine and setting (academic vs private practice), and/or on patient's preference. Approximately 20% of our study population were followed up by private practitioners who closely collaborate with the SHCS academic sites. It is therefore unlikely that this might have played an important role in the regimen choice. Additional arguments, such as drug costs or alternative treatment strategies (eg, intention-maintenance approach), might have influenced the initial decision making. However, in Switzerland, all people, including immigrants and asylum seekers, are insured by law. Therefore, the costs of antiretroviral drugs are not a major issue discussed for a specific patient and might not have influenced the choice of initial cART.

Our study has several strengths. To our knowledge, this is the first comprehensive prospective observational study investigating the choice of specific antiretroviral treatments and its associated factors, analyzing the prescription pattern of a large patient population, and comparing it with outcome. Moreover, different study sites used different preferred therapies in accordance with guidelines, allowing a comparison among many antiretroviral regimens used in clinical practice and investigating the influence of physicians' preference.

Obviously, the choice of regimen is based on a mixture of individualized concepts and on persistent misconceptions not supported by strong evidence. For example, boosted PIs were perceived as more potent than NNRTIs and were considered better choices for patients with advanced disease and high viral load. Personal experience and pathophysiologic concepts not analyzed in this study might also influence treatment strategies. Our study indicates that such choices and the notion of an individualized treatment must be confirmed in light of existing evidence.

In conclusion, large differences in prescription practices at different study sites but not in outcome were observed. A trend toward tailored cART was noted, suggesting that initial cART is significantly influenced by physician's preference and/or patient characteristics. Further studies evaluating the differences in effectiveness and tolerability of different regimens for different HIV-infected persons are needed.

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INVITED COMMENTARY

ONLINE FIRST

An Abundance of Choices

More than 25 antiretroviral drugs and fixed-dose combinations have been approved by the US Food and Drug Administration for the treatment of human immunodeficiency virus (HIV) infection in the 2½ decades since zidovudine (ZDV) became the first drug approved for this purpose. These drugs now constitute 6 different classes, including nucleoside and nucleotide reverse-transcriptase inhibitors (NRTIs), nonnucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand-transfer inhibitors, fusion inhibitors, and entry inhibitors. When used in appropriate combinations (usually 2 NRTIs plus a third drug from another class), these drugs achieve sustained suppression of viral replication, resulting in the arrest of disease progression and reconstitution of immune function. Such combination antiretroviral therapy (cART) has resulted in dramatic declines in HIV-associated morbidity and mortality wherever treatment is accessible.[1,2]

Although newer antiretroviral drugs with improved potency, safety, tolerability, and convenience have replaced many older drugs, patients and providers are faced with an abundance of choice in selecting a particular cART regimen. In this issue of the *Archives*, Elzi et al[3] explore the factors influencing choice of initial cART among adult patients followed up in the Swiss HIV Cohort Study (SHCS) as well as associated virologic and immunologic outcomes. They focused their study on partici-